

## Original article

## Seasonal and perennial allergic rhinitis: is this classification adherent to real life?

**Background:** Allergic rhinitis is traditionally subdivided into seasonal (SAR) and perennial (PAR), although the new definitions of persistent and intermittent were recently proposed. We assessed the validity of the traditional classification in a large group of subjects suffering from allergic rhinitis alone.

**Methods:** Young males referred to a Navy Military Hospital for routine fitness visit, and reporting symptoms of rhinitis alone were selected. According to the sensitization they were subdivided into (i) sensitized to pollens only (seasonal, SAR), (ii) to perennial allergens only (perennial, PAR) and (iii) to both (mixed, MAR). Spirometry, methacholine challenge, severity and characteristics of symptoms were assessed in all participants.

**Results:** Of 19 325 subjects, 2347 had allergic rhinitis. Seventy-two percent of the subjects had MAR, 17% SAR and 11% PAR. Ocular involvement and irritative symptoms were more frequent in SAR ( $P < 0.03$ ), whereas obstruction was predominant in PAR ( $P < 0.01$ ). Nasal symptoms varied according to the period of the year in SAR ( $P < 0.01$ ) and PAR ( $P < 0.03$ ). An overt bronchial obstruction was detected in 12% of PAR patients, in 7.8% of MAR, and in 4.2% of SAR. forced expiratory volume/1 s was significantly lower during season in SAR patients only ( $P < 0.05$ ). The FEF<sub>25–75</sub> was impaired in 22.5% MAR patients, 21% PAR, and 14% SAR, with a seasonal change in SAR ( $P < 0.05$ ) and PAR ( $P < 0.001$ ). Bronchial hyperreactivity was present in 82.2% of PAR, 73.6% of MAR, and 53.5% of SAR, with a seasonal change in SAR ( $P < 0.001$ ) and MAR ( $P < 0.05$ ).

**Conclusions:** This study provides evidence that up to 80% of allergic rhinitics have a mixed form, and SAR and PAR definitions are poorly adherent to real life. Lung involvement is frequent in patients reporting nose symptoms alone.

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Key words: bronchial hyperreactivity; bronchial obstruction; methacholine challenge; mixed allergic rhinitis; perennial allergic rhinitis; seasonal allergic rhinitis.

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Allergic rhinitis is the most frequent immunoglobulin (Ig)E-mediated disease. Its prevalence is high in the general population, and progressively increasing. Allergen exposure induces a cascade of inflammatory events that leads to the onset of symptoms. Typical nasal symptoms include itching, sneezing, rhinorrhea and obstruction. The first three of them are considered as 'irritative' phenomena, mainly because of histamine, whereas the nasal obstruction is predominantly related to the mucosal inflammation. Several studies have confirmed the strict association of allergic rhinitis with other allergic disorders, including asthma, conjunctivitis, and atopic dermatitis (1, 2). Moreover, it was shown that allergic rhinitis can be a risk factor for the onset of asthma, at least in adults (3).

Asthma is clinically characterized by bronchial inflammation and reversible airflow obstruction. The forced expiratory volume/1 s (FEV<sub>1</sub>) is the gold standard to quantify the airflow limitation. Presently, there is an

increasing interest about the role of small airways in asthma (4). It is true that there is no parameter equivalent to FEV<sub>1</sub>, capable to assess the functional status of small airways, but it was suggested that the forced expiratory flow between 25 and 75% of the vital capacity (FEF<sub>25–75</sub>) might be considered as a reliable evaluator of the calibre of distal airways, especially in subjects with normal FEV<sub>1</sub>. Bronchial hyperreactivity (BHR) is a paramount feature of asthma, and it can be detected also in a relevant proportion of rhinitics. In this regard, it has been hypothesized that a positive bronchial challenge to methacholine (MCh) in rhinitis patients can be considered a predictive factor for the development of asthma (5).

Allergic rhinitis is classically subdivided into seasonal (SAR) and perennial (PAR), according to the type of allergen and the occurrence of symptoms during the year (6, 7). Seasonal allergic rhinitis is mainly caused by outdoor allergens, such as pollens, whereas PAR is sustained by indoor allergens including house dust mites,

pets, and cockroaches. This classification has been recently revised by the Allergic Rhinitis and its Impact on Asthma (ARIA) workshop (8). The new classification of 'intermittent' and 'persistent' does not consider the type of allergen, but rather the duration of symptoms (days/week and consecutive weeks) of symptoms. Recently, one cross-sectional survey tested the ARIA classification against the classical one used in medical practice (9). The study reported that 43.7% of the patients, classified by doctors as seasonal, actually had persistent rhinitis, whereas 44.6% of those classified as perennial had intermittent rhinitis.

Based on these considerations, we studied a large group of subjects with clinical diagnosis of allergic rhinitis alone, subdivided them on the basis of the allergen, and evaluated the presence of ocular involvement, the type and severity of nasal symptoms and the pulmonary function both during and outside the pollen season.

## Material and methods

### Study design

This observational study was performed during the years 2000–2003, at the La Spezia Military Navy Hospital. The subjects were Navy soldiers referred for periodic fitness visit. The presence of symptoms of allergic rhinitis alone was carefully assessed. All the subjects underwent skin prick tests, pulmonary function test and MCh challenge. The study was approved by the Inner Review Board, and an informed consent was obtained from patients.

### Subjects and diagnosis

Among all subjects seen at the Navy Hospital, we enrolled in this observational study only those reporting symptoms of rhinitis with skin sensitization to pollens, perennial allergens or both. Those subjects reporting actual or past asthma symptoms (one or more of: persistent cough, wheezing, dyspnea, and shortness of breathing, either diurnal or nocturnal), were excluded. The diagnosis of allergic rhinitis was made on the basis of a history of nasal symptoms and positive skin prick test according with validated criteria (1). All the enrolled subjects underwent spirometry and MCh bronchial challenge.

On the basis of the sensitizing allergen we subdivided the patients into three groups:

- (a) sensitized to pollens only, SAR group;
- (b) sensitized to perennial allergens only, PAR group;
- (c) sensitized both to pollens and perennial allergens, MAR (mixed) group.

In our region the most relevant pollens are *Parietaria officinalis*, grasses, olive, birch and hazel, whereas the most important perennial allergens are house dust mites, cat, and dog (2).

As visits were performed over the whole years, we also considered two groups: those evaluated from March to September (i.e. during the period with high levels of pollens, arbitrarily considered pollen season) and those evaluated from October to February (period with very low pollen levels, arbitrarily considered as outside pollen season).

### Skin prick test

Skin tests were performed, with the common aeroallergens, according to the recommendations of the Italian Society of Allergy and Clinical Immunology (10). The allergen panel included: house dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*), cat, dog, grasses mix, Compositae mix, *P. officinalis*, birch, hazelnut, olive, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix. The concentration of allergen extracts was 100 IR/ml (Stallergenes, Milan, Italy). Positive (histamine 10 mg/ml) and negative (glycerol-buffer diluent of the allergen) controls were also used. Skin tests were applied on the volar surface of the forearm using 1 mm prick lancets (Stallergenes). The skin reaction was recorded after 15 min, and compared with the wheal of positive and negative controls. A wheal diameter  $\geq 3$  mm was considered positive. Antihistamines, if any, had to be withdrawn 1 week before skin prick test.

### Nasal and ocular symptoms

Patients were asked to self-evaluate the actual presence and severity of the following symptoms: nasal obstruction, sneezing, rhinorrhea, and itching. Each symptom was graded by the following scale: 0 = absent, 1 = mild (the symptom was not annoying or troublesome), 2 = moderate (troublesome symptom but not interfering with daily activity or sleep), and 3 = severe (the symptom was so severe to interfere with daily activity or sleep). The total symptom score (TSS) was the sum of the four symptoms. Symptoms were also subdivided into 'irritative' (itching, sneezing, and rhinorrhea), and 'obstructive'. The irritative symptom score was the arithmetical mean of the three mentioned symptoms. In addition the patients had to indicate whether one or more of the following symptoms were present at the moment: conjunctival redness, itching, lacrimation, and eyelids swelling.

### Pulmonary function test and methacholine bronchial challenge

Spirometry was performed by means of a computer-assisted spirometer (Pulmolab 435-spiro 235; Morgan Medical, Rainham, UK), with optoelectronic whirl flow meter. Spirometry was carried out according to the ERS guidelines (11). European Community for Steel and Coal (ECSC) reference values were used. If FEV1 was  $< 80\%$  of the predicted, a reversibility test was performed, with salbutamol 200  $\mu\text{g}$ . The reversibility test was considered positive when an increase in FEV1 of 12% or greater was achieved (12). Concerning FEF25–75, an increase of 15% or more from baseline values was considered for reversibility (13).

The MCh challenge was carried out only in those subjects with a normal baseline FEV1 ( $\geq 80\%$  of predicted). Methacholine was administered using a dosimetric computerized apparatus (MEFAR MB3; Marcos, Milan, Italy), activated by the inhalatory effort. Subjects inhaled progressively increasing doses of MCh (starting from 34 to 1590  $\mu\text{g}$ ) in 11 steps. The procedure was stopped when FEV1 fell by more than 20% from baseline. A computerized algorithm provided the provocation dose (PD20) value. If no response was obtained with the maximal cumulative dose of 1590  $\mu\text{g}/\text{ml}$ , the test was considered negative.

### Statistical analysis

Statistical analysis was performed using chi-square test, calculating confidential limits of the relative risk at 95%. Differences were

considered significant if  $P$ -values were  $< 0.05$ . Data are presented as mean  $\pm$  SD.

## Results

### Prevalence

19 425 consecutive subjects, aged  $22.7 \pm 4.4$  years, were seen at the Navy Hospital from 2000 to 2003. During the screening visit, diagnosis of allergic rhinitis alone was performed in 2347 subjects. Therefore, the overall prevalence of allergic rhinitis in the 4 years was 12.1%. Interestingly, looking at the prevalence year by year, a significant increase could be seen in the last 2 years, reaching 20.9% in 2003 (Table 1). All the eligible subjects with rhinitis agreed to participate to the study and signed an informed consent.

### Clinical aspects of allergic rhinitis

Based on the allergen, SAR was diagnosed in 405 patients (17%), PAR in 252 (11%), whereas 1690 (72%) had MAR (Table 2). The rate of MAR patients was as high as 80% in the last year of observation. The visits were equally distributed in the two considered periods: 55% during the pollination period and 45% out of the pollen season, considering that the duration of the two periods had the ratio of 7/5 months. The duration of rhinitis was  $< 12$  months in 25.4%, between 1 and 3 years in 41.2%,

Table 1. Prevalence of allergic rhinitis per year in absolute number and percentages

Year	Total visits	Total rhinitis	SAR (%)	PAR (%)	MAR (%)
2000	8590	935 (10.9)	200 (21)	89 (10)	643 (69)
2001	5732	537 (9.4)	101 (19)	53 (10)	384 (71)
2002	3247	487 (15)	56 (12)	79 (16)	353 (72)
2003	1856	388 (20.9)	48 (12)	31 (8)	310 (80)
Total	19 425	2347 (12.1)	405 (17)	252 (11)	1690 (72)

Table 2. Clinical and functional features in seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and mixed allergic rhinitis (MAR) patients

Features	SAR	PAR	MAR
Prevalence	17%	11%	72%
Ocular involvement	64.9%	46.4%	47.9%
'Irritative' symptoms	2.7	1.2	1.8
'Obstructive' symptoms	1.4	2.8	2.2
TSS seasonal variation	Yes	Yes	No
FEV1 $< 80\%$	4.2%	12%	7.8%
FEV1 seasonal variation	Yes	No	No
FEF25–75 $< 80\%$	14%	21%	22.5%
FEF25–75 seasonal variation	Yes	Yes	No
BHR % of patients	53.6%	82.2%	73.6%
BHR seasonal variation	Yes	No	Yes

TSS, total symptom score; FEV1, forced expiratory volume/1 s; BHR, bronchial hyperreactivity.

between 3 and 10 years in 19.1% and more than 10 years in 14.3% of the subjects. Allergic conjunctivitis was significantly more frequent in SAR (64.9%) than in PAR (46.4%) and MAR (47.9%,  $P < 0.03$ ). Irritative symptoms were more frequent in SAR patients than in the other groups ( $P < 0.01$ ), whereas obstruction was significantly more severe in PAR patients in comparison with SAR group ( $P < 0.01$ ). No significant difference was detectable in the MAR group (Fig. 1).

There was a significant difference in TSS depending on the period both in SAR and PAR patients. The SAR patients had a significant increase of TSS during the pollen season ( $P < 0.001$ ), and PAR patients showed more intense symptoms during the October–February period ( $P < 0.03$ ). No significant variation could be seen in MAR patients (Fig. 2).

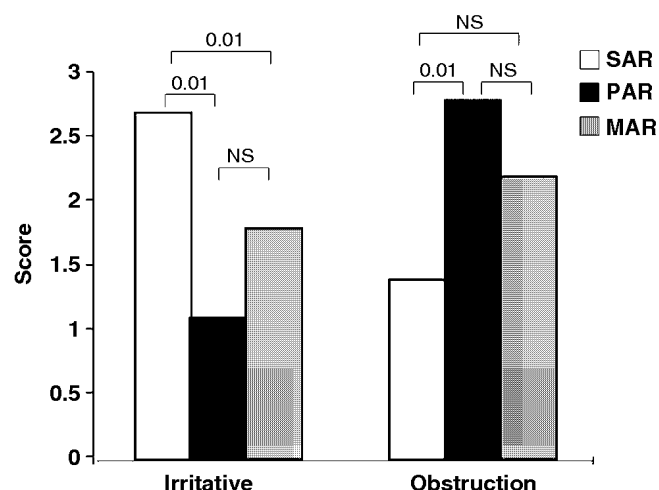


Figure 1. Scores for irritative symptoms and obstruction in patients with seasonal allergic rhinitis, perennial allergic rhinitis, and mixed allergic rhinitis.

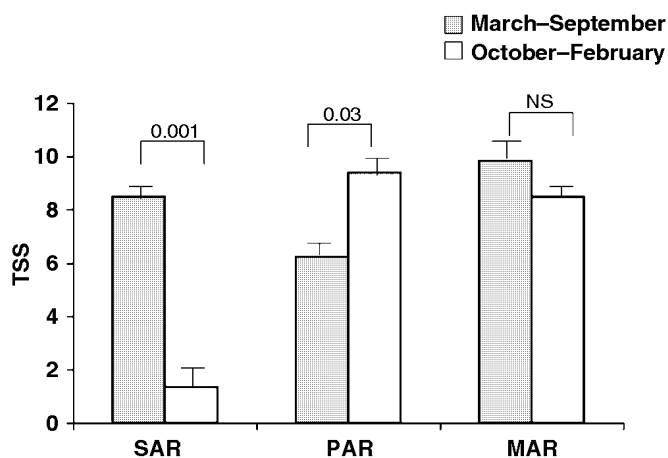


Figure 2. Total symptom score in patients with seasonal allergic rhinitis, perennial allergic rhinitis, and mixed allergic rhinitis during the March–September period (gray bars) and the October–February period (white bars).

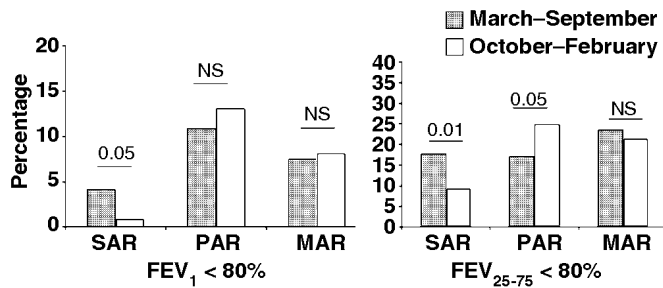


Figure 3. Percentages of patients showing FEV<sub>1</sub> values <80% of predicted (left) and FEV<sub>25-75</sub> values <80% of predicted (right) during the March–September period (gray bars) and the October–February period (white bars).

#### Pulmonary function test and methacholine challenge

As all subjects reported only nasal symptoms, the occurrence of overt bronchial obstruction (i.e. FEV<sub>1</sub> < 80% predicted) was unexpectedly high: 4.9% of SAR, 12% of PAR and 7.8% of MAR patients. Figure 3 shows the distribution of rhinitis with FEV<sub>1</sub> values <80% of predicted. There was a seasonal variation in SAR patients only ( $P < 0.05$ ). As well as for FEV<sub>1</sub>, also the FEV<sub>25-75</sub> was low in a consistent percentage of rhinitis as reported in Fig. 3. Interestingly, a seasonal variation of this parameter was detectable both in SAR ( $P < 0.05$ ) and PAR patients ( $P < 0.001$ ). It is noteworthy the inverse behavior of SAR and PAR: SAR subjects had a greater flow impairment (FEV<sub>1</sub> and FEV<sub>25-75</sub>) during the March–September period, whereas PAR patients were more obstructed during the October–February period. The MAR patients did not show any seasonal variation. Overall, a nonspecific BHR could be detected in 53.6, 82.2 and 73% of SAR, PAR and MAR respectively. There was a significant difference between SAR and PAR patients ( $P < 0.001$ ) and between SAR and MAR patients ( $P < 0.003$ ), whereas there was no

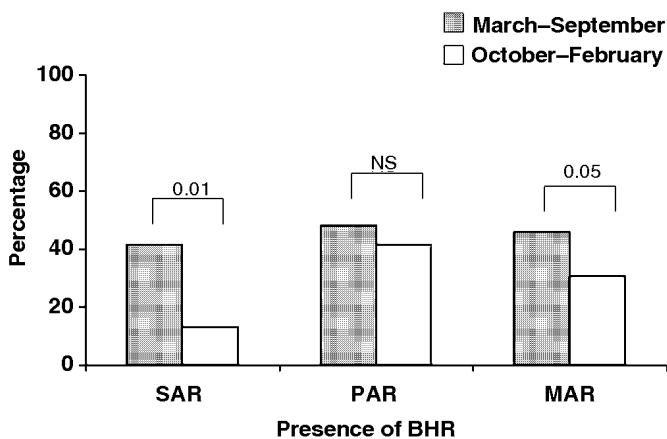


Figure 4. Percentages of patients with perennal allergic rhinitis, seasonal allergic rhinitis, and mixed allergic rhinitis showing bronchial hyperreactivity during the March–September period (gray bars) and the October–February period (white bars).

difference between PAR and MAR patients. Concerning the seasonal variation of BHR, there was a significant variation both in SAR patients ( $P < 0.001$ ) and MAR patients ( $P < 0.05$ ) as reported in Fig. 4.

#### Discussion

The diagnosis of allergic rhinitis is based on the association of clinical history and IgE sensitization. The classical definition of SAR and PAR relies mainly on the type of allergen involved and on the distribution of symptoms during the year. This presumes that the seasonal type is related to pollens, whereas the other one involves perennial allergens. Nevertheless, this classification is not completely satisfactory in the everyday clinical practice. In fact: (a) some plants have a long-lasting pollination, (b) some patients allergic to perennial allergens have symptoms only for short periods, (c) the pollination season is highly variable among the different countries, (d) there is a high percentage of polysensitized patients, (e) an allergic inflammation can be present even in the absence of symptoms (the so-called minimal persistent inflammation). These are the reasons why the ARIA Workshop changed the classification into intermittent and persistent rhinitis (8). A recent study confirmed that the ARIA classification is more appropriate (9) than the traditional one.

We performed a study on a large population of subjects perceiving only nasal symptoms, in order to evaluate the clinical and functional aspects with respect to the types of allergic rhinitis and the causal allergen(s). The overall prevalence of allergic rhinitis over a 4-year period was 12%, but it reached 20% in the last year (2003) of observation. This finding is in agreement with those reported in larger epidemiological surveys (14, 15), although in our study the diagnosis of AR was substantiated by skin prick tests, not simply based on questionnaires. Interestingly, in the majority of patients allergic rhinitis had a very recent onset (66% in the last 3 years). This demonstrates that allergic disorders are really increasing from an epidemiological point of view. We observed that allergic conjunctivitis and irritative (histamine-mediated) symptoms occurred more frequently in SAR patients, whereas obstructive symptoms were more typical of PAR patients. Moreover, a seasonal variability of the symptom score was detectable both for SAR and PAR patients (SAR patients have more symptoms during spring–summer, PAR patients worsen during autumn–winter) whereas MAR patients did not show seasonal variations. Indeed, the most important finding of our study is that the large majority of subjects (80% in 2003) exhibited a MAR, as they were sensitized both to seasonal and perennial allergens. We can conclude that some differences really exist between SAR and PAR, but in the clinical practice they are present only in a minority of cases, and MAR, which is persistent, is the most

frequent type of allergic rhinitis. Thus, our data confirm the validity of the ARIA classification that is based on the duration of symptoms rather than on the type of allergen.

As the persistence of allergic inflammation closely depends on the allergen exposure also in symptomless patients (16), MAR typically represents the model of persistent rhinitis also from a pathophysiologic point of view. On the contrary, both SAR and PAR show preferentially a seasonal behavior, although opposite: SAR is predominant during the pollen season, PAR during the fall. *Dermatophagoides* have in fact seasonal variation linked to humidity and indoor temperature. However, as pollen season may be prolonged for some pollens (e.g. *Parietaria*), symptoms do not disappear completely even during the cold season.

Another important aspect is the lung involvement. Overall, 7.5% of the subjects, reporting only allergic rhinitis, had overt bronchial obstruction, thus confirming that asthma is underdiagnosed (17) or, in alternative, that some patients are 'poor perceiver'. On the contrary, the number of patients with overt bronchoconstriction was greater in the PAR and MAR groups outside the pollen season. This is probably because of the increased amount of mites during the autumn–winter period. Thus, there is close relationship between level of allergen exposure and bronchial airflow impairment. Moreover, BHR was

present in about 50–80% of the subjects, that is more than previously reported in other studies (18, 19). Also in this case, a relationship between the period of allergen exposure and BHR was demonstrated. Considering the FEF25–75 it was shown that a fraction of rhinitics had bronchial airflow impairment. It is noteworthy that this percentage diminished outside the pollen season in SAR patients, but did not completely disappear. This is consistent with the concept that chronic bronchial inflammation as well as BHR may persist also in absence of allergen exposure. Moreover, in PAR and MAR patients this parameter appears more impaired outside the pollen season. These facts are in agreement with the recent concept of the link between upper and lower airways: allergic rhinitis and asthma should be considered two clinical manifestation of a disorder involving the whole respiratory tract (20, 21), and the two disorders are strictly interdependent (22, 23).

Our findings suggest that also those patients reporting 'pure' allergic rhinitis should be carefully investigated for the involvement of the lower respiratory tract. When possible, considering the costs and availability, spirometry should be performed, especially in those patients with persistent symptoms (PAR or MAR). Bronchial MCh challenge may be considered as supplemental test to achieve a more exhaustive evaluation in rhinitics.

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